Ref N. Application # 09/784,980

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 9/14, 9/10

A1

(11) International Publication Number: WO 94/05260

(43) International Publication Date: 17 March 1994 (17.03.94)

(21) International Application Number: PCT/US92/07513

(22) International Filing Date: 3 September 1992 (03.09.92)

(71) Applicant: AFFINITY BIOTECH, INC. [US/US]; 305 Chelsea Parkway, Boothwyn, PA 19061 (US).

(72) Inventors: YIV, Seang, H. ; 800 Rockwood Road, Wilmington, DE 19802 (US). TUSTIAN, Alex, K. ; 27-H Highland Boulevard, New Castle, DE 19720 (US).

(74) Agents: ELDERKIN, Dianne, B. et al.; Woodcock, Washburn, Kurtz, Mackiewicz & Norris, One Liberty Place - 46th floor, Philadelphia, PA 19103 (US).

(81) Designated States: AU, CA, JP, RU, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE).

Published
With international search report.
With amended claims and statement.

(54) Title: TASTE-MASKING PHARMACEUTICAL COMPOSITIONS AND METHODS FOR MAKING THE SAME

(57) Abstract

A method of masking the flavor of a drug which is present in particulate form and the drug composition produced therefrom is provided. A drug, in particulate form, which has an unpalatable taste is mixed with a lipid. To this drug/lipid mixture is added an emulsifying agent, a polymer solution and a sweetening dilution solution to provide the final stable drug composition.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BG	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic			SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovak Republic
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	UA	Ukraine
DE	Germany	MG	Madagascar	US	United States of America
DK	Denmark	ML	Mali	UZ	Uzbekistan
ES	Spain	MN	Mongolia	VN	Viet Nam
FI	Finland				

TASTE-MASKING PHARMACEUTICAL COMPOSITIONS AND METHODS FOR MAKING THE SAME

Field of the Invention

This invention relates to techniques for taste-masking pharmaceutical drugs. More specifically, the invention relates to compositions comprising a drug having its taste masked by a lipid coating contained within an aqueous polymer system for oral administration which provides an improved taste for the drug.

Background of the Invention

It is well known that many medicaments intended for oral administration are highly unpalatable because of their bitter taste. Sweeteners have been added to these medicaments in order to mask the unpleasant taste, however, sweeteners alone are insufficient to entirely mask the bitter taste of many drugs.

A more recent and convenient means of preparing these drugs is in a granule lipid format which avoids the storing of the drug in an aqueous solution which solution could destroy the lipid coating. The granules are usually suspended in an aqueous solution immediately prior to oral administration and, in this manner, the drug is not dissolved in the mouth of the patient, but rather passes on to the gastro-intestinal tract where it is dissolved by stomach fluids. By storing the drug within an integral coating of a lipid a granule format, the drug can be maintained in its flavor masked form for at least 14 days and maybe longer.

Lipid coatings for masking the bitter taste of

certain drugs have been beneficially employed as is shown in U.S. Patent No. 4,865,851 to James et al and U.S. Patent No. 4,764,375 to Paradissis. However, these references describe processes which require producing granules of the lipid coated drug, which processes require special processing equipment to produce the granules. The James et al. reference describes the use of providing a lipid coating onto cefuroxime axetil by use of a spray drying technique. Such a technique for coating the drug requires specific spray drying equipment and is relatively an expensive and intricate process. The drug used in James necessitated an integral lipid coating and storage in the granule state because the drug would gel in an aqueous carrier solution. The Paradissis reference describes the use of a lipid coating to coat potassium chloride. Again, the drug is stored in the granule state which requires assorted equipment to accomplish that process. The potassium chloride is highly water soluble and therefore must be kept in the granule state because the drug and integral lipid taste-masking coating break down within minutes in an aqueous state.

A need therefore exists to provide a drug composition and a method for preparing the same in which a drug which has an unpalatable taste is presented in a taste-masked form wherein the drug composition is in a readied state for oral administration, can be stored in such a stable state, and does not require additional formulation immediately prior to oral administration.

Summary of the Invention

A method of producing a stable drug composition which masks the flavor of a drug in need of flavor masking is provided which is broadly defined by the following steps. A drug in particulate form is mixed with a lipid at a temperature below that where significant drug degradation occurs, preferably below about 50°C. To this drug and lipid mixture is added an emulsifier, a polymer solution, and a

dilution solution to form the stable taste-masked drug composition.

In an alternative embodiment, the method proceeds as follows. A mixture of a lipid and an emulsifier are heated until that mixture is brought into a molten state. The lipid and emulsifier mixture temperature is then adjusted to a temperature below that where significant drug degradation occurs, preferably below about 50°C. To this cooled mixture is then admixed the drug, in particulate form, which thereby forms a flavor masked drug/lipid dispersion. To this drug dispersion is supplied a polymer solution to form a concentrated drug composition. Finally, a dilution solution, preferably comprising a sweetening agent, is added to form the final drug composition.

Preferably, the drug is selected from the group consisting of cimetidine, ranitidine, ibuprofen, acetaminophen, and erythromycin. The method of the present invention provides a stable dispersion of the drug, in a flavor masked state, which dispersion has an extended shelf life of several months.

Certain preferred particular embodiments of the invention are also disclosed. The drug to lipid weight ratio ranges from about 1:0.25 to about 1:2. Also, the drug is preferably added in amount up to about 800 milligrams per 10 milliliters (10 cc) of the drug composition. In another preferred embodiment of the invention, the polymer is supplied as a polymer solution which contains the polymer in an aqueous solution and preferably contains carboxymethylcellulose and xanthan gum.

The invention also provides for the drug compositions produced by the inventive methods.

Detailed Description of the Invention

The present invention broadly relates to a novel and economical method of preparing a stable pharmaceutical composition which contains a drug, which is characterized by having an unpleasant taste, wherein the drug is provided in a flavor masked form in a dispersion system. The invention provides for the effective flavor masked encapsulation of the drug in a lipid material and for the suspension of this drug/lipid component in an aqueous phase with the aid of emulsifiers and suspending agents. The drug composition produced also contains an aqueous phase comprising a polymer system and additive agents such as sweeteners and flavor enhancers. The final drug composition is a dispersion which is believed to be stable indefinitely. Stability has been demonstrated from as short as a day up to as long as 3 months in its flavor masked state. The drug composition is generally stored at a temperature range of from about 4°C to about 40°C, preferably at about 15°-25°C, and most preferably at room temperature.

The methods by which the pharmaceutical compositions are produced are described as follows. In one embodiment, the drug, which is in particulate form, is mixed by conventional methods with the lipid at a temperature below where degradation of the drug can significantly occur. This degradation is evidenced by a substantial inactivation of the drug and is readily determined. The temperature is typically kept below about 50°C to avoid the degradation of the drug at higher temperatures for most drugs. The lower temperature limit of the lipid is governed by the ability to thoroughly mix the drug in the lipid. The lipid can be either a paste or a liquid and it is preferred that the lipid be in a liquid state to aid in the drug admixing. An emulsifier, a polymer solution and a dilution solution are then mixed with the drug/lipid mixture to form a the final stable taste-masked drug composition. This final drug composition contains the drug, partially coated with the lipid and effectively taste-masked by the lipid, suspended in the polymer solution. It

is preferred that the emulsifier be thoroughly admixed first, followed by the addition of the polymer solution, and the final drug volume achieved by addition of the dilution solution. However, these three components can be admixed together with the drug/lipid mixture. The final drug composition is in a form which can be administered to a patient orally.

The inventive method can also be carried out by a different method. First, a mixture of a lipid and an emulsifier is heated and mixed by conventional methods until a molten homogenous state is reached. Preferably, the temperature of the molten lipid will be at least about 20°C above the melting point of the lipid and typically will be in the range of from about 50°C - 100°C. The temperature of this lipid and emulsifier mixture is then adjusted to a temperature below where significant drug degradation can occur, typically below about 50°C, in order to accept the drug without degrading the integrity of the drug. A drug in need of taste masking, in particulate form, is added to the lipid and emulsifier mixture which can be in the form of a semi-solid paste or a liquid. Then, a polymer is admixed to this dispersion. Finally, a dilution solution, preferably an aqueous solution containing, for example, sweetening agents and/or flavoring agents and/or coloring agents is added to the mixture to produce the final drug composition.

In order to produce the taste-masking pharmaceutical compositions suitable for oral administration, the melting point of the lipid should be sufficiently high to prevent melting of the substantially coated particles during the short period of time they are contacted with the mouth. Such melting would release the unpleasant taste. There potentially is no upper limit to the melting point of the lipid. The lipids will conveniently have a melting point of from about 30°C to about 95°C. It is preferred to select a lipid which allows for an effective amount of the drug to be released upon digestion, and most preferably to select a lipid which does not affect the bioavailability of the drug.

The lipids which can be employed in the practice of the present invention include triglycerides, for example a glycerol ester of a high molecular weight (C_{10-30}) aliphatic acid; fatty acids or monohydric alcohols thereof, fixed oils, fats, waxes, sterols, phospholipids and glycolipids. The lipid may also, for example, be a high molecular weight straight chain (C_{10-30}) saturated or unsaturated aliphatic acid, hydrogenated and partially hydrogenated oils such as cotton seed oil, castrol oil, and coconut oil; waxes, for example, bees wax or carnauba wax; mixtures of high molecular weight fatty acids such as mixtures of stearic and palmitic acids, and mixtures of high molecular weight straight chain aliphatic alcohols. A preferred lipid is a partially hydrogenated coconut oil sold by Karlshams Company under the trade name PURECO 92.

The emulsifiers, or surfactants, which are useful in the practice of the present invention maybe of the anionic or nonionic type. The emulsifier of the present invention can be a mixture of several emulsifiers. A mixture of an anionic and a nonionic emulsifier is preferred as the emulsifying agent. Examples of emulsifiers include acids, for example, stearic acid, lauric acid, palmitic acid, etc.; glyceryl behenate, and monooleates, such as sorbitan monooleate and polyoxyethylene sorbitan monooleate. Preferred emulsifiers include anionic surfactant such as a diacetyl tartaric acid monoglyceride, for example, those sold under the trade name PANODAN 205 and SDK by the Grinsted Company. Also, a preferred nonionic surfactant is glycerol stearate, for example, LIPOGMS 470 manufactured by Lipo Chemical Company.

Drugs in need of taste masking are those drugs which have an unpleasant taste when orally administered and include cimetidine, ranitidine, ibuprofen, acetaminophen, erythromycin and the like. Cimetidine is conveniently preferred. The method of the invention provides a highly convenient and economical method of taste-masking certain unpleasant tasting drugs. However, the drug is believed to be substantially coated but not entirely coated by the lipid. Thus certain

drugs, such as cifuroxime axetil which tend to gel upon contact with an aqueous medium are not suitable for use in the invention. The drug is supplied in particulate form, and preferably has a weight average particle size below about 300 microns, most preferably below about 200 microns in order to avoid a gritty taste upon consumption. The drug preferably has a low water solubility and the pH of the composition can be adjusted to enhance this aspect of the invention.

The polymers which are useful in the present invention are added to keep the lipid encapsulated drug in suspension and for thickening and include cellulose derivatives such as sodium carboxymethylcellulose as well as xanthan gum. One particular sodium carboxymethylcellulose for use in the present invention is a low molecular weight AQUALON 7LF PH manufactured by the Aqualon Company. It is preferred to provide the polymer in an aqueous solution. It is also preferred to add a substance to aid in the dissolution of the polymer in the aqueous solution, such as glycerin.

The dilution solution is preferably an aqueous solution and functions to dilute the concentrated drug emulsion to an acceptable level for oral administration. Various sweeteners, flavoring agents, and coloring agents can also be added to the dilution solution. Basically, the dilution solution is a sugar solution in a concentrated form, for example, above about 50% by weight of sweetener. The various sweeteners include sucrose, sodium cyclamate, sodium saccharinate, aspartame and ammonium glycyrrhizinate. Typical flavoring agents include peppermint oil flavor and artificial pineapple flavor. Examples of coloring agents include titanium dioxide pigments, lake colors and iron oxide pigments.

Other suitable additives are included within the scope of the invention, such as an antacid to a cimetidine preparation.

The pharmaceutical drug composition of the present invention can be formulated in any desired quantities. In order to more fully describe the present invention, a basis

of 10 cc of the final stable taste-masked drug composition can be used to define weight and volume ratios. Typical oral administration volumes range from about 5 cc to 15 cc. The amount of the drug to be added to a 10 cc solution of the drug composition of the present invention is from about 100 to 800 milligrams of the drug. Once the amount of drug to be added has been determined, the amount of lipid to be used can readily be determined. Typically, the amount of lipid ranges from 25-200% by weight of the amount of drug employed. In a preferred embodiment, the ratio of drug to lipid is 1:1. However, the maximum amount of lipid to be added to a 10 cc solution of the drug composition is about 800 milligrams. The amount of emulsifier to be used in the present invention varies depending upon the type of emulsifier utilized. An effective amount of emulsifier is needed however to provide a drug composition which exhibits extended shelf life. In a preferred embodiment, the amount of emulsifier is generally from about 0.3-3% by weight of the drug composition. The amount of polymer to be added to a 10 cc solution of the drug composition of the present invention generally ranges from about 30 milligrams to about 120 milligrams. The dilution sweetening agent solution (containing also the flavoring and coloring agents) generally is added in an amount to bring the volume of the drug composition to the 10 cc quantity.

In a more detailed embodiment of the invention, the method for producing the drug composition of the present invention comprises five broad steps. In the first step, the weighed amount of lipid and emulsifier are mixed together and heated into a molten solution up to about 20°C above the melting point of the lipid. It is preferred that the temperature of the molten solution be from about 85-95°C. The lipid and emulsifier are mixed until a homogenous liquid phase is formed.

The second step requires for the molten solution to be cooled. It is preferred that the solution be cooled to at least 50°C or below to avoid drug degradation, but such that the mixture remains a liquid or a semi-solid paste.

In the next step, the weighed amount of the drug to be used is added to this cooled lipid phase. The drug and lipid phase are mixed thoroughly using any appropriate mixing device. In this way, the drug particles are substantially coated with the lipid material whereby a flavor masking effect is obtained as at least a portion of the drug is contained within the lipid phase and has its flavor masked by the lipid phase.

To this drug/lipid phase is added an appropriate amount of the polymer, i.e. an amount of polymer sufficient to suspend the lipid coated particles and provide the desired thickness. The polymer is preferably added as polymer solution. This polymer solution is an aqueous solution in which the polymer is dissolved. If a non-aqueous solution is chosen it is to be compatible with the lipid. Preferably, the polymer is present in the polymer solution in an amount of from about 6% to about 10% by weight. This solution may also contain glycerin in an amount of about 20% by weight to aid in the dissolution of the polymer. The polymer solution is thoroughly mixed into the drug/lipid phase by the aid of mechanical mixing devices.

In the last step, a sweetening dilution mixture is slowly added to the drug composition to enhance the flavor of that composition. Preferably, this sweetening solution is added in a concentrated form and contains sweetening agents, flavoring agents, and coloring agents. The sweetening solution is an aqueous base solution and is added to the drug composition until the final drug composition attains its desired volume.

INVENTIVE EXAMPLE 1

70mg of Panodan 205, 50mg of Lipo GMS 470, and 400mg of Pureco 92 were weighed into the same vessel, and heated to about 90 degree centigrade until clear homogeneous liquid phase was formed. This lipid phase was allowed to cool to room temperature at which point it becomes a semisolid paste. To this lipid phase was added cimetidine (400mg). This

mixture was mixed until homogeneous. To this drug-lipid mixture was added polymer solution (8%w/v 7LF PH, 20%w/v Glycerin, 788 mg). This mixture so obtained was mixed until homogeneous. To this mixture was added the sucrose solution (65%w/w sucrose, 0.05%w/v methyl parabens; 10.560g), a spearmint oil flavor (2.8mg), a peppermint oil flavor (1mg), and the mixture was mixed until homogeneous. The product so obtained was a viscous syrup with a pH of 7.7 containing 400mg of cimetidine per approximately 10ml of liquid. This product has improved taste over the non-inventive formulation.

INVENTIVE EXAMPLE 2

Panodan 205 (90mg) and Pureco 92 (400mg) were mixed and heated to about 90 degree centigrade until a homogeneous liquid was formed. This lipid phase was allowed to cool to room temperature. Cimetidine (400mg) was added to this lipid phase. The mixture so obtained was mixed until homogeneous. To this drug-lipid mixture was added polymer solution (8%w/v CMC 7LF PH, 20%w/v Glycerin; 788mg). The mixture so obtained was mixed until homogeneous. To this mixture was added the sucrose solution (65%w/w sucrose; 10.75g), Methyl parabens (5mg), artificial pineapple flavor (3mg) and color (5%w/v FD&C yellow #5; 2.5mg). This composition has a pH of 7.4 and contains approximately 400mg cimetidine in 10ml of liquid.

INVENTIVE EXAMPLE 3

Lipo GMS 470 (100mg), stearic acid (100mg) and Pureco 92 (400mg) were mixed and heated to 90 degree centigrade until a homogeneous liquid was formed. The other ingredients were mixed in the same amount and in the same way described in inventive example 2. This composition has a pH of 7.6 and contains about 400mg cimetidine in 10mg of liquid.

INVENTIVE EXAMPLE 4

Lipo GMS 470 (200mg) and Pureco 92 (400mg) were mixed and heated to 90 degree centigrade until a homogeneous liquid phase was formed. The other ingredients were mixed in

the same amount and in the same way described in inventive example 2, except that flavor and color were not added. This composition has a pH of 8.1 and contains about 400mg cimetidine in 10mg of liquid.

INVENTIVE EXAMPLE 5

Panodan 205 (47mg), Lipo GMS 470 (33mg) and Pureco 92 (267mg) were mixed and heated to about 90 degree centigrade until a homogeneous liquid was formed. This lipid phase was allowed to cool to room temperature. Cimetidine (267mg) was added to this lipid phase. The mixture so obtained was mixed until homogeneous. To this drug-lipid mixture was added a CMC solution (8%w/v CMC 7LF PH, 20%w/v Glycerin; 788mg) and a Xanthan Gum solution (Keltrol from Kelco 2%w/v, Glycerin 20%w/v; 150mg). The mixture so obtained was mixed until homogeneous. To this mixture was added the sucrose solution (65%w/w sucrose; 11.07g), Methyl parabens (5mg). This composition has a pH of 7.7 and contains approximately 266mg cimetidine in 10ml of liquid.

INVENTIVE EXAMPLE 6

Lipo GMS 470 (150mg), Cottonseed oil (338mg) and glycerol behenate (112mg) were mixed and heated to about 90 degree centigrade until a homogeneous liquid was formed. This lipid phase was allowed to cool to room temperature. Cimetidine (400mg) was added to this lipid phase. This mixture so obtained was mixed until homogeneous. To this drug-lipid mixture was added a CMC solution (8%w/v CMC 7LF PH, %w/v Glycerin; 788mg). The mixture so obtained was mixed until homogeneous. To this mixture was added the sucrose solution (65%w/w sucrose; 10.75g), Methyl parabens (5mg), citric acid solution (10%w/v; 130mg), and artificial pineapple flavor (4mg). This composition has a pH of 7.1 and contains approximately 400mg cimetidine in 10ml of liquid.

INVENTIVE EXAMPLE 7

100ul of Panodan SDK, 600ul of Nestle Choco-bake were mixed and heated to about 90 degree centigrade until a

clear homogeneous liquid phase was formed. This lipid phase was allowed to cool to room temperature at which point it becomes a semisolid paste. To this lipid phase was added cimetidine (400mg). This mixture was mixed until homogeneous. To this drug-lipid mixture was added a polymer solution (4%w/v 7LF PH, 10%w/v Glycerin; 1000ul). The mixture so obtained was mixed until homogeneous. To this mixture was added the sucrose solution (65%w/w sucrose, 0.05%w/v methyl parabens; 7.9ml) and a peppermint oil flavor (0.7ul), and the mixture was mixed until homogeneous. The product so obtained was a viscous syrup containing 400mg of cimetidine per approximately 10ml of liquid.

INVENTIVE EXAMPLE 8

50ul of Panodan SDK, 50ul of stearic acid and 600ul of Nestle Choco-bake were mixed and heated to about 90 degree centigrade until a clear homogeneous liquid phase was formed. The other ingredients were mixed in the same amount and in the same way described in inventive example 7. The product so obtained was a viscous syrup containing 400mg of cimetidine per approximately 10ml of liquid.

INVENTIVE EXAMPLE 9

Panodan 205 (32mg), Lipo GMS 470 (32mg) and Pureco 92 (200mg) were mixed and heated to about 90 degree centigrade until a homogeneous liquid was formed. This lipid phase was allowed to cool to room temperature. Acetaminophen (320mg) was added to this lipid phase. The mixture so obtained was mixed until homogeneous. To this drug-lipid mixture was added polymer solution (8%w/v CMC 7LF PH, 20%w/v Glycerin; 788mg). The mixture so obtained was mixed until homogeneous. To this mixture was added the sucrose solution (65%w/w sucrose; 11.26g). Sodium benzoate (10mg) and citric acid (40mg). This composition has a pH of 3.8 containing approximately 320mg acetaminophen in 10ml of liquid.

INVENTIVE EXAMPLE 10

Panodan 205 (50mg), Lipo GMS 470 (50mg) and Pureco 92 (300mg) were mixed and heated to about 90 degree centigrade until a homogeneous liquid was formed. The other ingredients were mixed in the same amount and in the same way described in inventive example 9, except that the amount of citric acid was 50mg and of sucrose solution was 11.05g. This composition contains approximately 320mg acetaminophen in 10ml of liquid.

What is claimed:

1. A method of producing an aqueous stable drug composition which masks the flavor of a drug in need of taste-masking, consisting essentially of the steps of:

(a) mixing the drug in particulate form into a lipid at a temperature below where significant drug degradation occurs; and

(b) adding an emulsifier, a polymer and an aqueous dilution solution to the mixture of step (a) to form the aqueous stable taste-masked drug composition.

2. A method of producing an aqueous stable drug composition which masks the flavor of a drug in need of taste-masking, consisting essentially of the steps of:

(a) heating a mixture of a lipid and an emulsifier until the mixture is in a molten state;

(b) adjusting the temperature of the mixture below where significant drug degradation occurs;

(c) admixing to the mixture the drug in particulate form;

(d) adding a polymer solution to the mixture of step (c) to form a concentrated drug composition; and

(e) diluting the concentrated composition with an aqueous dilution solution to produce the stable taste-masked drug composition.

3. The method of claims 1 or 2 wherein the drug is selected from the group consisting of cimetidine, ranitidine, ibuprofen, acetaminophen, and erythromycin.

4. The method of claim 1 wherein the temperature is maintained below about 50°C.

5. The method of claims 1 or 2 wherein the drug to lipid weight ratio is from about 1:0.25 to about 1:2.

6. The method according to claims 1 or 2 wherein the drug is present in a concentration of less than 800 mg per 10 cc of the drug composition.

7. The method according to claims 1 or 2 wherein the emulsifier is present in an amount of from 0.3 to 3% by weight of the drug composition.

8. The method according to claims 1 or 2 wherein the polymer is added in the form of an aqueous solution and comprises a cellulose derivative or xanthan gum.

9. The method according to claim 8 wherein the aqueous polymer solution is added after the emulsifier is thoroughly mixed with the lipid and drug mixture.

10. The method according to claims 1 or 2 wherein the dilution solution comprises a sweetening agent.

11. The method of claim 2 wherein the temperature of step (a) is in the range from 50-100°C and the temperature of step (b) is adjusted to about 50°C or below.

12. A method of producing a stable cimetidine drug composition which masks the flavor of cimetidine, consisting essentially of the steps of:

(a) heating a mixture of a lipid and an emulsifier until the mixture is in a molten state;

(b) adjusting the temperature of the mixture to about 50°C or below;

(c) admixing to the mixture cimetidine in particulate form;

(d) adding a polymer solution to the mixture of step (c) to form a concentrated drug composition; and

(e) diluting the concentrated composition with an aqueous dilution solution to produce the stable taste-masked drug composition.

13. The method according to claim 12 wherein the temperature of step (a) is in the range from about 50-100°C.

14. The method of claim 12 wherein the dilution solution comprises a sweetening agent.

15. The method according to claim 12 wherein the cimetidine to lipid weight ratio is from about 1:0.25 to about 1:2.

16. The method according to claim 12 wherein the cimetidine is present in a concentration of less than 800 mg per 10 cc of the drug composition.

17. The method according to claim 12 wherein the emulsifier is present in an amount of from 0.3 to 3% by weight of the drug composition.

18. The method according to claim 12 wherein the cimetidine drug composition, on a 10 cc volume basis, the cimetidine is present in an amount of from 400-800 mg, the lipid is present in an amount of from 200-800 mg, the emulsifier is present in an amount of from 0.3 to 3% by weight of the cimetidine composition, and the polymer is present in an amount of from 30-120 mg.

19. The method according to claim 12 wherein the polymer comprises a mixture of carboxymethylcellulose and xanthan gum.

20. The method according to claim 12 wherein the lipid and emulsifier are heated to a temperature of about 85-95°C.

21. A stable drug composition produced by the process of claims 1, 2, or 12.

AMENDED CLAIMS

[received by the International Bureau on 5 October 1993 (05.10.93); original claims 1-21 replaced by amended claims 1-20 (5 pages)]

1. A method of producing an aqueous stable drug composition which masks the flavor of a drug in need of taste-masking, consisting essentially of the steps of:

(a) mixing the drug in particulate form into a lipid at a temperature below where significant drug degradation occurs; and

(b) adding an emulsifier, a polymer and an aqueous dilution solution to the mixture of step (a) to form the aqueous stable taste-masked drug composition.

2. A method of producing an aqueous stable drug composition which masks the flavor of a drug in need of taste-masking, consisting essentially of the steps of:

(a) heating a mixture of a lipid and an emulsifier until the mixture is in a molten state;

(b) adjusting the temperature of the mixture below where significant drug degradation occurs;

(c) admixing to the mixture the drug in particulate form;

(d) adding a polymer to the mixture of step (c) to form a concentrated drug composition; and

(e) diluting the concentrated composition with an aqueous dilution solution to produce the stable taste-masked drug composition.

3. The method of claims 1 or 2 wherein the drug is selected from the group consisting of cimetidine, ranitidine, ibuprofen, acetaminophen, and erythromycin.

4. The method of claim 3 wherein the drug to lipid weight ratio is from about 1:0.25 to about 1:2.

5. The method according to claim 3 wherein the drug is present in a concentration of less than 800 mg per 10 cc of the drug composition.

6. The method according to claim 3 wherein the emulsifier is present in an amount of from 0.3 to 3% by weight of the drug composition.

7. The method according to claim 3 wherein the polymer is added in the form of an aqueous solution and comprises a cellulose derivative or xanthan gum.

8. The method according to claim 7 wherein the aqueous polymer solution is added after the emulsifier is thoroughly mixed with the lipid and drug mixture.

9. The method of claim 2 wherein the temperature of step (a) is in the range from 50-100°C and the temperature of step (b) is adjusted to about 50°C or below.

10. A method of producing a stable cimetidine drug composition which masks the flavor of cimetidine, consisting essentially of the steps of:

(a) heating a mixture of a lipid and an emulsifier until the mixture is in a molten state;

(b) adjusting the temperature of the mixture to about 50°C or below;

(c) admixing to the mixture cimetidine in particulate form;

(d) adding a polymer solution to the mixture of step (c) to form a concentrated drug composition; and

(e) diluting the concentrated composition with an aqueous dilution solution to produce the stable taste-masked drug composition.

11. The method according to claim 10 wherein the temperature of step (a) is in the range from about 50-100°C.

12. The method according to claim 10 wherein the cimetidine to lipid weight ratio is from about 1:0.25 to about 1:2.

13. The method according to claim 10 wherein the cimetidine is present in a concentration of less than 800 mg per 10 cc of the drug composition.

14. The method according to claim 10 wherein the cimetidine drug composition, on a 10 cc volume basis, the cimetidine is present in an amount of from 400-800 mg, the lipid is present in an amount of from 200-800 mg, the emulsifier is present in an amount of from 0.3 to 3% by weight of the cimetidine composition, and the polymer is present in an amount of from 30-120 mg.

15. The method according to claim 10 wherein the polymer comprises a mixture of carboxymethylcellulose and xanthan gum.

16. The method according to claim 12 wherein the lipid and emulsifier are heated to a temperature of about 85-95°C.

17. A stable drug composition produced by the process of any of the proceeding claims.

18. An aqueous stable drug composition which masks the flavor of a drug in need of taste-masking, comprising, on a 10 ml basis, about 100 to about 800 mg of a drug selected from the group consisting of cimetidine, ranitidine, ibuprofen, acetaminophen, and erythromycin; from about 25 to about 800 mg of a lipid; from about 30 to about 120 mg of a polymer; and wherein the composition further comprises from about 0.3-3% wt. of a surfactant.

19. The aqueous drug composition of claim 18 wherein the drug comprises cimetidine.

20. The aqueous composition of claims 18 or 19 wherein the polymer comprises a cellulose derivative or xanthan gum.

STATEMENT UNDER ARTICLE 19

Replacement pages 14-18 submitted herewith contain claims 1-20 which replace the originally filed claims 1-21. Claim 2 has been amended to more properly define the addition of step (d). Claim 4 of the originally filed claims has been deleted. Claims 5-9 of the originally filed claims have been renumber as present claims 4-8 and the claimed dependency of renumbered claims 4-7 has been changed to claim 3. Originally filed claims 12-21 have been amended in that originally filed claims 14 and 17 have been deleted and the remaining claims have been renumbered correspondingly. Originally filed claim 21, now claim 17, has been amended to depend upon the entirety of the method claims. Claims 18-20 of the newly filed claims further define certain preferred embodiments of the compositions set forth in the present application.

Replacement page 18 is submitted herewith as a bland page 18, to reflect that claim 21 has been cancelled and no longer appears on this page.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/07513

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 9/14, 9/10
US CL :424/494, 496; 514/974
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/494, 496; 514/974

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS: Taste-masking, lipids, fats, xanthan, carboxymethylcellulose, surfactants, emulsifiers cimetidine, sweet, sucrose, saccharine, aspartane drugs, dispersions, syrups

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US, A, 4,865,851 (JAMES) 12 SEPTEMBER 1989 column 4, lines 19-51, column 5, lines 57-68, column 6, lines 1-65, column 3, line 58 and column 5, line 24, column 10, line 56, column 5, line 42.	1,2,5,6,8,10,11,21 4,7,9 12-20
Y	US, A, 4,894,233 (SHARMA) 16 JANUARY 1990 Examples 1 and 7, column 3, lines 1-48, column 4, lines 9-42, column 25-65, column 7, line 25 through column 9, line 22, column 11, lines 7-59	1-21
Y	US, A, 4,676,984 (WU) 30 JUNE 1987 column 6, lines 48-55.	3, 12-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 16 FEBRUARY 1993	Date of mailing of the international search report AUG 04 1993
Name and mailing address of the ISA/ Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer NEIL LEVY Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)★